Title: The Primary Ciliary Dyskinesia Foundation Network for Clinical Trials (PCDF NCT): Proposals for Founding Regional Hub-Centers (Development Phase)

Summary of Purpose: To invite applications from academic medical centers in the United States to join the development phase for the Primary Ciliary Dyskinesia Foundation Network for Clinical Trials (PCDF NCT). The PCDF NCT is envisioned as a catalyst to facilitate efficient, effective clinical trials, observational and translational research programs, patient engagement, and quality improvement initiatives leading to improved care, treatments, and cures for patients and families affected by PCD.

Key Dates

- Opportunity Announcement: May 23, 2025
- Letter of Intent Due: June 13, 2025

  A Letter of Intent is required, containing the following elements:
  - Names of partner institutions
  - Names, credentials and role(s) of key personnel
  - Contact information for the contact PI (email, phone, address)
  - Estimated numbers of adult (≥ 18yo) and pediatric (<18yo) patients with PCD seen regularly for clinical follow-up at the institution(s) - broken down by each partner institution as applicable
  - Clarification of any special circumstances or permissions that may be needed, as indicated in the text of the opportunity below

  Letters of Intent should be addressed to the PCD Foundation and emailed as a PDF attachment to Kristen Wavell-Shifflett (KristinWS@pcdfoundation.org)
- Application Due Date: July 15, 2025
- Awardees Notified and Public Announcement: Quarter 4 - 2025
- Earliest Start Date: February 1, 2026

Full Text of Announcement

Section 1: Funding Opportunity Description

Background: Primary ciliary dyskinesia (PCD) is a rare genetic disorder that affects multiple organ systems. This rare disease is associated with laterality defects and congenital heart conditions, infertility, and an inability to effectively clear mucus and infectious organisms from the upper and lower airways, leading to serious progressive respiratory, sinonasal, and otological disease over time.

The exact number of people affected by PCD is unknown, and we continue to identify patients with this rare disease and novel genes associated with this disease. While it was previously believed that only ~15,000 patients in the US had PCD, recent genetic discoveries and analyses have revealed that about 1 in 7,500 individuals are predicted to have the disease in the US (~45,000 in total; Hannah *et al.* 2002).

Because it is rare and heterogeneous in its presentation and diagnosis requires specialized expertise, PCD is historically underdiagnosed. Currently, there is limited data on how the disease progresses over time; however, associations between different genotypes and clinical progression are starting to be uncovered. Population-level morbidity and mortality data are not yet available, but we know that irreversible lung damage, bronchiectasis, and functional impairment lead to serious morbidity and a shortened lifespan.

There is no cure or FDA-approved therapies for PCD. Most management strategies are derived from treatments used in patients with other respiratory diseases, like asthma and cystic fibrosis (CF), but without proven efficacy in PCD.

Inspiration: Today's story of PCD closely mirrors the story of CF). In the 1950s, a child born with CF had a limited lifespan. Now, the average life expectancy of a person with CF is close to 60 years. With newer revolutionary therapies on the market, an infant born today with CF may live a relatively normal and long life. These advances in CF care were made possible by the Cystic Fibrosis Therapeutics Development Network (CFTDN). Since its inception in 1998, the CFTDN has partnered with pharmaceutical companies, government, academia, and individual researchers to develop and trial novel therapeutics, confirm best management practices, and increase awareness and diagnosis of CF. The remarkable success of the CFTDN in a disorder with similar features to PCD provides a blueprint for the PCDF NCT to achieve similar results for individuals with PCD.

Challenges: As a rare disease, there are typically only a small number of patients with PCD followed at any single clinical center, and only a limited set of clinical-research programs across the United States have the specialized infrastructure required to conduct meaningful clinical trials in this rare disease. Previous attempts to conduct trials in PCD have been met with challenges stemming from regulatory hurdles, inadequate protocol design, difficulties with recruitment, insufficient access to research personnel, excessive delays in site contracting, and other barriers. Due to these historic challenges, many pharmaceutical companies are unwilling to invest in the risky proposition of developing new treatments for PCD. This situation closely resembles the challenges faced by the CF community before the inception of the CFTDN.

The Solution: Replicating the model of the CFTDN, the PCD Foundation is leading the creation of the PCDF NCT ('the Network'). The Network will provide solutions to the challenges inherent in PCD research, mitigate risks in investment in therapeutic development, and ensure access to clinical research for people with PCD, researchers, and industry. The Network will provide a streamlined, centralized approach to PCD clinical research in the United States, leading to continuous improvements and efficiencies in the conduct of clinical research and trials through shared knowledge of best practices, rapid identification of emerging therapeutic targets and outcome measures, and standardization of processes across research centers.

Key aspects of the Network will include

- Co-design of research protocols in partnership with Network experts
- Centralized, standard operations
    - Financial/contracting, regulatory, data quality, and safety monitoring
    - Clinical coordination: standardized operating procedures with centralized training, quality assurance and oversight, and over-reading for specialized testing procedures
- Access to clinical centers with stable, PCD-specific infrastructure and access to patients
- Partnership with the PCD Foundation
    - Patient Advisory Board
    - PCDF Patient Contact Registry
    - PCDF Research Registry
    - PCDF Programmatic and Support Staff
- Access to the PCD Biorepository
    - Historic samples for preliminary data generation
    - Sample curation and storage
    - Centralized sample analysis
- Providing opportunities for:
    - People and families affected by PCD to engage in research and advocacy
    - Early career physicians and scientists to gain expertise in PCD and research
    - Advancing critical basic and translational research

Organization and Scope: The PCDF NCT is a clinical research network consisting of three distinct entities:

- The Leadership Center (LC), which will be housed at the University of North Carolina at Chapel Hill (UNC-CH) and serve as the clinical and administrative coordinating center for the Network
- The Regional Research Centers (RRC), which will initially consist of 2 – 4 additional academic medical centers geographically dispersed across the United States
- The PCD Foundation, which will serve as the sponsor of the Network during the initial development phase

Building upon the clinical research infrastructure and partnership between the Genetic Disorders of Mucociliary Clearance Consortium (GDMCC; NCATS/NHLBI U54HL096458) and the PCD Foundation over the past two decades, the PCDF-NCT will be a partnership among the LC, RRCs, and PCDF with the ultimate goal of bringing new cures and treatments to patients and families affected by PCD.

The LC will drive overall strategy, administrative/fiscal management, and clinical coordination of supported initiatives. RRCs will contribute expertise and leadership to the Network (i.e. Steering Committee membership, protocol development and selection, Network services and scientific core development, etc) and support selected Network initiatives and research protocols. The PCD Foundation will provide input on Network priorities and access to PCDF resources, such as the PCDF Contact Registry and Research Registry, as well as patient representatives.

Network leadership will include the LC and RRC PIs, key support staff, and PCDF representatives. Over the first 12-18 months, the Network will focus on capacity building (establishing policies, procedures, financial and other legal agreements, building essential Network services and core operations, etc) and engaging Network partners with the ultimate objective of being in an optimal position to empower large, industry-sponsored clinical trials focused on patients with PCD.

While the Network is primarily targeted toward enabling PCD-focused research in the form of clinical trials sponsored by pharmaceutical partners, it will be fully committed to enhancing the overall infrastructure for PCD research across the United States. To this effect, the Network will undertake Network-directed research initiatives (e.g. NIH-funded investigator-initiated research) and create mechanisms that allow non-Network investigators and institutions to engage the Network as a collaborating partner and/or resource across the full translational research spectrum (basic/pre-clinical, clinical & population, and implementation research). Contingent upon Network progress and assessment of available opportunities, it is anticipated that Network investigators may engage in proposal development for funding of one or more clinical research projects as early as 6 months after Network launch.

Structure and Requirements of PCDF NCT Regional Research Centers

The RRCs will participate in development, leadership, and operational support aspects of the Network. During the initial Development Phase, it is anticipated that:

RRC investigator(s) will:

- Play active roles in Network committees and working groups
- Actively push and oversee required institutional contracting and regulatory agreements
- Engage in research protocol and network policy development as needed
- Identify opportunities and contribute to and/or lead proposal development involving the Network
- Help disseminate awareness of and foster collaborative partnerships within the Network

RRC Support staff will:

- Support RRC investigators to accomplish all facets of their responsibilities as described above
- Join and contribute to appropriate Network committees and working groups focused on clinical coordination and operational aspects of the Network
- Ensure full engagement of the site in PCDF-sponsored initiatives such as the PCD Research Registry
- Help establish protocols, policies, and create required training materials for the Network

Budget, Number of Awards, Renewals, and Required Personnel

The described budget and personnel requirements are meant to address the anticipated needs of the Network solely in support of development activities over the first 18-24 months. Awards will be disseminated yearly, with renewal for the second year determined through an evaluation process directed by the Network Steering Committee and the ultimate decision held by the Network Executive Leadership Council. Full award amounts may change year by year, based on available sponsor funds, modification of Network activities, other available resources, etc. The PCD Foundation's goal is to provide stable financial support for the program for at least the first 5 years of operation, allowing the Network time to develop contracts, partnerships, and secure independent funding mechanisms to ensure the financial independence and sustainability of the Network.

The initial funding period will be a 12-month term. Applicants may request up to $125,000 USD in total costs, inclusive of a 10% cap on indirect rates set by PCD Foundation policy. Applicants may submit as a consortium of two or more geographically linked partner institutions. A single sub-award between the primary applicant and another geographically-linked clinical research center with a complementary adult and/or pediatric PCD program is allowable. Collaborative applications identifying a need for additional sub-awards should include an explanation in their LOI or email the PCDF.

Each application should identify:

- Co-Lead Investigators who are clinical team members of the RRC's respective Adult and Pediatric PCD programs will oversee the program, with one serving as the contact PI for RFA-related communications. This individual should be a member of the submitting institution. Each Co-Lead Investigator shall commit at least 10% FTE toward the Network activity described in this RFA.
- Any number of additional co-investigators may be included. No minimal effort is stipulated, but any co-investigator will be expected to play an active role in the developing Network-attending Network meetings, contributing to one or more steering committee/working groups, etc).
    - *See required Letters of Support in Section II*
- One lead clinical research coordinator to support the local program, with at least one additional research coordinator at each additional partnering institution as applicable. (25% minimal effort is anticipated by the lead research coordinator. No minimum is stipulated for additional coordinators or any other programmatic staff committed to the Network.)

Two to four awardees will be selected to participate as Regional Research Centers for the initial 12 months of the Network. Additional opportunities to join the Network will be offered in subsequent RFAs.

Additional financial support to engage in Network activities beyond the description of "Network development activities" as engendered within this RFA and codified within policy to be determined early upon Network initiation will be provided as needed and as negotiated between the Network and relevant sponsor(s). Such activities would include specific clinical research projects, clinical trials, or other targeted activities with a specified operational scope, an external source of funds (e.g. NIH award,

industry contract, additional PCDF or other non-profit award, etc), and approval by the Network Steering Committee.

Section II – Eligible Institutions and Individuals

Applications may be submitted by any major academic medical center (university–hospital partnership) within the United States. *Non-US-based North American institutions will be invited to apply to join the Network in a future RFA.*

Only one application will be accepted from any institution. Institutions applying as a consortium may only be members of a single application.

Applicant institutions must

- Be members in good standing of the PCD Foundation Clinical and Research Centers Network (PCDF-CRCN). *Applicants may request special dispensation to allow consideration if they are currently co-applying/under consideration to join the PCDF-CRCN at the time of submission.*
- Be active contributors to the PCDF Research Registry
- Have pediatric and adult PCD clinical programs

Lead investigators must

- Have the skills, knowledge, and resources necessary to carry out the proposed work to:
    - Contribute meaningfully to the development activities of the Network
    - Transition to serving as *de facto* site-principal investigator or overall lead principal investigator for future clinical research projects that the Network engages in, as determined by the Network Steering Committee.
- Have a demonstrable record of engagement in PCD-focused clinical research within the past 5 years
- It is anticipated that Lead Investigators will be holders of an M.D., D.O., or other related clinical doctorate-level degrees. *Applicants proposing other types of degree-holders in the Lead Investigator position should seek permission before completing an application.*

Section III – Application Components

1. **Biographical Sketches** – An NIH-formatted biographical sketch must be submitted for the Lead Investigator(s) and all other investigators and/or key personnel (as defined by the NIH).
2. **Letters of Support**
    - Institutional Leadership Representatives (Required): At least one letter from each participating institution is required and should come from the relevant Departmental Chair and/or a Dean directly overseeing the proposed Lead Investigator(s). This letter must affirm protection of the time committed to the Network for each named investigator, assure the accuracy of the required data regarding clinical trials execution for item #4 below, and outline the institution's commitment to fostering the development of the Network.
    - Additional named co-investigators (Required): Each named co-investigator beyond the Lead Investigator(s) must provide a letter of support stipulating their commitment to the Network in the form of an statement of agreement to attend and contribute to Network Steering Committee meetings as non-voting members and contribute to at least one Network initiative (working group, network committee, etc.) if called upon by the Steering Committee to do so. (up to ~5% FTE equivalent effort is expected to satisfy these requirements). The letter should

succinctly outline related expertise or interest the investigator has in the developing Network and may refer to the investigator's provided Biosketch as applicable.

- Other Letters (Optional but encouraged): Letters from clinicians, researchers, or other potential network partners affiliated with the applicant(s) and supportive of the Network's development are encouraged. These letters should outline the expertise, resources, and/or ideas of the supportive individual/group as related to potential future involvement in the Network.

3. **Relevant Publications List** – Provide a list of PCD-related and/or other rare disease publications over the previous 10 years by investigators at the RRC. The names of the Lead Investigator(s) and any other named investigator of the RRC should be **bolded and underlined**. Other faculty *currently* at the RRC institution and providing a letter of support should have their names **bolded** only. Publications involving named RRC investigators that were not conducted at the proposed RRC site(s) should be denoted with an * at the end of the entry.

   Other publications involving the RRC center(s) that do not include a named RRC investigator may be listed in a separate section at the bottom of the list. An explanation for each publication in this category should be provided (2-3 sentences should suffice).

4. **IRB Approval Process and Clinical Trials Contracting** – Provide data in a tabular format showing information for the last 10 clinical trials that the RRC's *applicable (adult v. peds)* pulmonary division(s) have conducted as the administering unit. If submitting as a consortium, a table is required for each participating center.

   The Table should display:

   - Start and Stop Year of the trial at the site
   - Trial name and NCT#
   - Primary Sponsor(s)
   - Names of investigators involved at the site. Designate the lead site PI with an asterisk*.
   - Disease(s) under study
   - Key Inclusion/Exclusion criteria – (allowable ages, particularities of inclusion/exclusion criteria; full EC/IC do not need to be listed)
   - Time between site selection and finalization of contract/clinical trial agreement
   - Time between receipt of study protocol/documents and IRB approval
   - Time between site activation and first enrolled participant
   - Enrollment – Enrolled participants / Initial Target Enrollment
   - Optional text explaining particularities related to this trial
     Alternative list format may be used if a table becomes unwieldy as long as the data elements are included and easily identifiable

5. **Site Leadership and Institutional Environment** – **PCD-focused Clinical and Research Infrastructure (12 pages max, ½ in margins, 11pt font, inclusive of figures/tables**– Description of the proposed PCDF NCT Research Regional Hub site, including:
   - The leadership team and key supporting staff members: include a description of each team member's clinical and research expertise focused on PCD, respiratory, and/or rare diseases. Highlight work and/or leadership positions within research consortia or large, multi-center clinical trials.
   - A breakdown of patients available locally at the site:

i. Numbers and detailed demographic (age, race, biological sex) breakdown of PCD patients by diagnosis status (clinical diagnosis only, genetically confirmed diagnosis, non-genetically confirmed diagnosis *i.e.* ciliary ultrastructure defect confirmed) that have been seen for regular clinical follow-up at the site within the past 2 years.

- Describe the PCD-focused clinical and research infrastructure currently in place at the site:
    i. Clinical Program (Adult and Pediatric) – key services integrated into the program (e.g. cardiology, immunology, genetics and counseling, ENT/audiology, respiratory therapy, specialized clinical diagnostic testing, pulmonary function testing, radiology and imaging, etc). Note the track record of any relevant fellowship programs available at the center that may benefit from the Network.
    ii. Research Program:
        1. A high-level summary of the PCD research initiatives, programs, and expertise the site has engaged in over the past 5 years.
            a. For each program/initiative/project – provide the names of major lead personnel involved (investigators - indicate if they are no longer at the site), a description of the program and how the site was involved, the number of enrolled participants (if applicable), and any other informative detail.
            b. For the PCDF Research Registry – please indicate the number of enrolled pediatric and adult patients that the proposed RRC site(s) have enrolled and any relevant commentary
            c. Note any specialty research testing/facilities that may be available at the site and applicable to PCD research. *i.e. mucociliary clearance testing, novel chest and paranasal sinus imaging modalities, unique laboratory-based or other types of research infrastructure, specialized pulmonary function testing, specialized training/certification of personnel (e.g. overreading capacity), etc*
        2. Include information on any additional institutional infrastructure available to support PCD-focused research which may be applicable (personnel, core services, etc). Indicate how these resources have been engaged in PCD-research in the past (if applicable).
    iii. Any additional relevant information highlighting the proposed RRC site/collaborative's advantages as a Development Phase PCDF NCT Regional Research Center.
    iv. Applicants should provide brief (limited to 1 page) commentary and ideas regarding the development of the Network (vision/goals/governance structures/services/etc) and keen areas of research/development which should be prioritized to enhance clinical trial readiness in PCD.

Section IV – Network Governance

The full governance structure for the Network will evolve over time, according to the needs and priorities of the Network. Here we describe a summary of plans for the initial outset of the Network. Detail available upon request by contacting Kristin Wavell-Shifflet (KristinWS@pcdfoundation.org).

1. **Executive Leadership Council (ELC)** - The ELC will provide strategic and programmatic oversight in defining and ensuring the long-term strategy of the network through resource allocation, partnership development, and network expansion. The ELC will have responsibility for financial oversight, monitoring of network and site performance, and coordination of network infrastructure (i.e. administrative, data management, and regulatory coordination).
2. **Network Steering Committee (NSC)** – Will advise the ELC on all facets of Network operations with a focus on fostering scientific collaboration, trial/protocol implementation and coordination, and handling site-level concerns. The NSC will be comprised of all members of the Executive Leadership Council plus the Adult and Pediatric Leads of each RRC. Additional representatives of the PCDF team may be assigned as voting- or non-voting members of the NSC at the discretion of the ELC.
3. **Additional Governance Structures** – As the network develops, sites are added, and opportunities help drive Network priorities, we envision that additional governance and working groups will be required to ensure efficient operations of the

SECTION V – Year 1 Objectives

We will utilize the roadmap of the CF-TDN to help fast-track our initial set of Network objectives within the first year of the program. Our initial objectives are to establish key Network governance structures, cooperative agreements between the LC, RRCs, PCDF, and the overall Network as a quasi-independent entity (goal), and attract or generate a moderate-to-large-scale clinical research project/trial that will help catalyze additional Network development.

- Establish Initial Network LC and RRC Sites (2-4 sites in total)
- Policy and Protocol Creation focused on:
    - Governance for the Network, Interactions with Industry and Other Sponsors
        - Formalize initial governance structure, identify and populate additional working groups; populate and conduct two meetings with the External Advisory Board Committee
        - Establish proposal/study review processes
    - Establishing agreement frameworks between PCDF, UNC/LC, RRC-sites, and the Network as an entity
        - Data sharing/coordination, protocol review, site monitoring, and financial arrangements
        - Standard operating procedures for routine procedures and outcome measures used in PCD clinical research/trials
        - Establishing cost estimates and unified charges for future network negotiations
        - Interactions with PCDF resources (Registry collaboration/data requests, patient advocacy representative contributions, etc)
- Setting up LC infrastructure:
    - Trial and Network management (administrative and clinical-research data management; communications and milestone tracking; central-IRB establishment and regulatory documentation; procedures for site evaluation, training, and initiation; financial administration for future trials)
    - Shared Sponsor-LC collaboration framework for overseeing trials
- Opportunity Development

    - Outreach to engage industry and academic collaborators focused on informing them about the growing network and engagement in future projects
    - Network/Investigator-initiated research proposal development
- Network Expansion
    - Develop opportunities to engage additional clinical research sites as Network partners
    - Standardize site evaluation and selection processes